

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 18 NOV 2005

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| Applicant's or agent's file reference 21726-97440 | | FOR FURTHER ACTION | | See Form PCT/PEA/416 |
| International application No. PCT/US2004/030986 | | International filing date (day/month/year) 22.09.2004 | Priority date (day/month/year) 22.09.2003 | |
| International Patent Classification (IPC) or national classification and IPC A61K38/17, C07K14/47 | | | | |
| Applicant BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS | | | | |
| <p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 12 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau) a total of 2 sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input checked="" type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p> | | | | |
| <p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input checked="" type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p> | | | | |
| Date of submission of the demand 22.07.2005 | | Date of completion of this report 17.11.2005 | | |
| Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | | Authorized Officer Griesinger, I Telephone No. +49 89 2399-7596 | | |



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2004/030986

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-51 as originally filed

Claims, Numbers

1-20 as originally filed

Drawings, Sheets

1/40-40/40 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing *(specify)*:
 - ☐ any table(s) related to sequence listing *(specify)*:
4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☒ the claims, Nos. 1-16
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing *(specify)*:
 - ☐ any table(s) related to sequence listing *(specify)*:

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 13-15

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 13-15 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. -

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
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Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
- ☐ restricted the claims.
 - ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ neither restricted nor paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|-------------------------|
| Novelty (N) | Yes: Claims | 9,10,12,16-18 |
| | No: Claims | 1-8,11,19,20 |
| Inventive step (IS) | Yes: Claims | none |
| | No: Claims | 1-12,16-20 |
| Industrial applicability (IA) | Yes: Claims | 19,20 |
| | No: Claims | 1-18 (opinion reserved) |

2. Citations and explanations (Rule 70.7):

see separate sheet

Introduction

The present communication refers to the following documents (D) cited in the international search report.

- D1: AL-ZOUBI ADEEB M ET AL: "Contrasting effects of IG20 and its splice isoforms, MADD and DENN-SV, on tumor necrosis factor alpha-induced apoptosis and activation of caspase-8 and -3" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 276, no. 50, 14 December 2001 (2001-12-14), pages 47202-47211, XP002317870 ISSN: 0021-9258
- D2: EFIMOVA ELENA V ET AL: "Differential effects of IG20 and its splice isoform, DENN-SV, on cell proliferation and apoptosis" FASEB JOURNAL, vol. 16, no. 5, 22 March 2002 (2002-03-22), page A1083, XP009044048 & ANNUAL MEETING OF PROFESSIONAL RESEARCH SCIENTISTS ON EXPERIMENTAL BIOLOGY; NEW ORLEANS, LOUISIANA, USA; APRIL 20-24, 2002 ISSN: 0892-6638
- D3: EFIMOVA ELENA V ET AL: "IG20, in contrast to DENN-SV, (MADD splice variants) suppresses tumor cell survival, and enhances their susceptibility to apoptosis and cancer drugs." ONCOGENE, vol. 23, no. 5, 5 February 2004 (2004-02-05), pages 1076-1087, XP002317873 ISSN: 0950-9232

The application relates to the splice variants IG20 and DENN-SV which are both encoded by the gene *IG20*. Other splice variants of the same gene are called KIAA0358, DENN and MADD. It is shown that overexpression of the splice variant IG20 in HeLa cells results in growth attenuation and higher susceptibility for apoptosis induced by TNF-alpha or by radiation, whereas overexpression of DENN-SV enhances resistance to apoptosis and increases cell division. The use of said splice variants or of the corresponding antisense molecules or antibodies or SiRNA to regulate cell death or cell replication is claimed.

D1 discloses that IG20, KIAA0358, MADD/DENN, and DENN-SV are different splice variants of the same gene, which was designated *IG20*. HeLa cells stably transfected with IG20 showed enhanced susceptibility to TNF-alpha-induced apoptosis, whereas cells transfected with DENN-SV showed resistance. MADD/DENN did not alter the susceptibility to TNF-alpha-induced apoptosis.

D2 is an abstract disclosing that IG20 is expressed in seven different isoforms in various combinations in both normal and cancer cells and tissues. Furthermore, it is disclosed that HeLa cells transfected with IG20-isoform showed slow growth and enhanced TNF-alpha induced apoptosis, while the cells transfected with the isoform DENN-SV showed high proliferation and increased resistance to apoptosis. Similar effects were found when cells were treated with vinblastin, etoposide, or gamma irradiation.

D3 was published prior to the international filing date but later than the priority date claimed (PX document). D3 seems to be the scientific publication of the application. It has not been considered in the present written opinion, since it was published after the priority date of the present patent application and regulations concerning such "PX" documents differ between the PCT member states. However, the document may be relevant for accessing novelty and inventive step of the present application.

Re Item I

Basis of the opinion

The present report has been established as if the claims had not been amended, since the amendments have been considered to go beyond the disclosure of the application as originally filed (Rule 70.2 c PCT).

Amended claim 1 is directed to a composition comprising the splice variants IG20 or DENN-SV or a fragment of said splice variants or an "agent" which decreases or increases DENN-SV levels. Said claim may be understood comprise any composition with one of the above-listed compounds e.g. in water or a buffer. However, a composition comprising an "agent" which decreases or increases DENN-SV levels is not disclosed in the application as originally filed. In particular, original claim 17 can not form the basis for amended claim 1, since a product claim is considered to be broader than a method claim. Consequently, amended claim 1 and the thereon dependent claims 2-4 go beyond the disclosure of the application as originally filed. Independent of the observation that such a composition is not disclosed in the application as originally filed, the "agent" is not considered to fulfill the requirements of Articles 5 and 6 PCT (see observations for original claims 17 and 18).

Furthermore, independent claim 11 seems to go beyond the disclosure of the application

as originally filed, since said claim is also directed to a method using a combination of the splice variants IG20 and DENN-SV. The use of such a combination does not seem to be disclosed anywhere in the application as originally filed.

For clarity purpose, the present communication only refers to the claims as originally filed. However, the arguments also apply for the amended claims. Only the last paragraph of the present communication under the title "further observations" refers to both the claims as originally filed and the amended claims.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Original claims 1-18 could be interpreted as method of treatment of the human/animal body. For the assessment of the above-mentioned claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. In other cases, the restriction of the claims to an *in vitro* method would allow industrial application in view of the EPO.

2. The terms "IG20" and "DENN-SV" and splice variants thereof are not clear (Article 6 PCT). Said terms only seem to be used in scientific publications of the inventors and are not a recognized designation of the gene. For example, the terms are not present in the OMIM database of NCBI (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>). Furthermore, Applicant's attention is drawn to the fact, that at least according to the practice of the EPO, reference to database accession numbers such as in paragraph 90 on page 20 of the description and in claims 19 and 20, are not considered to clearly define the proteins, since the database entries change over time due to constant updates of the databases. Therefore, only a database accession number in combination with information to the database and the relevant date are considered to be sufficiently clear.

Furthermore, it is confusing that the term "IG20" is used not only to refer to the splice variant but also to the gene and that the claims do not indicate that DENN-SV is also a splice variant of the gene IG20.

In addition, the antibodies, anti-sense and Si RNA molecules are not clearly defined. In view of the overlapping sequences of the different isoforms of the gene IG20, it seems to be essential to define the region of the gene to which said molecules bind or correspond. This opinion is confirmed by the statement on page 8, paragraph 31 that only Si RNA molecules to the middle portion of DENN-SV have the desired effect.

Finally, the description clearly indicates that IG20 and its splice variants have opposite effects: It is shown that overexpression of IG20 in HeLa cells results in growth attenuation and higher susceptibility for apoptosis induced by TNF-alpha or by radiation, whereas overexpression of DENN-SV enhances resistance to apoptosis and increases cell division. D1 also discloses the above-mentioned effects of IG20 and DENN-SV and in addition that the splice variants MADD/DENN did not alter the susceptibility to TNF-alpha-induced apoptosis. In view of said different effects of splice variants, it seems to be necessary to restrict each claim to one specific isoform and a specific use of said isoform based on the effect disclosed in the description. Hence, claims to the use of not further defined splice variants or fragments thereof do not seem to be allowable, since the skilled practitioner does not know, which effect said splice variants or fragments will have (see also non-unity objection). Said problem is further emphasised by the fact, that DENN-SV may be considered to be a splice variant of the splice variant IG20 (see e.g. Figure 2).

3. Original claim 13 is directed to the suppression of cell replication in tumor cells using DENN-SV. This claim seems to contradict the observed effect that DENN-SV enhances resistance to apoptosis, i.e. favours cell replication. In view of said contradiction, no examination of said claim can be performed:

4. Original claims 14 and 15 are not clear (Article 6 PCT). It seems that the binding to a specific receptor of the splice variants of IG20 is an intrinsic property of the proteins, i.e. indirectly already claimed in claim 1. Furthermore, it seems that the splice variants may bind to different receptors and therefore, the definition of binding of any splice variant to any receptor is confusing. Furthermore, claim 15 seems to be intended to define said

receptors. However, the list refers to FAS-*ligand*, TNF-alpha, TRAIL and anti-receptor antibodies, wherein no member of the list is considered to be a receptor. In any case, claims 14 and 15 seem to be superfluous. Since the intended scope of claims 14 and 15 is not clear, no examination can be performed.

5. Original claims 17 and 18 are neither clear nor supported by the description nor sufficiently disclosed (reach through claims), since the "molecule to regulate endogenous levels of IG20 or at least one of its splice variants" (see claim 17, part (a)) is not known. According to claim 18, which is dependent on claim 17, it may be any "chemical regulator, genetic sequence, cDNA, oligonucleotide, protein, peptide or fragments thereof, and antibodies", without referring to any structural features. Hence, the matter for which protection is sought is not clearly defined. A compound should be clearly and unambiguously defined by technical features and not by the result to be achieved. Furthermore, the subject-matter of the aforementioned claims does not seem to be disclosed in the description in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 5 PCT). The only molecules which are sufficiently clear are anti-sense molecules, Si RNA molecules and antibodies of IG20 and its splice variants. Therefore, examination has been restricted to said molecules.

Re Item IV

Lack of unity of invention

The application as filed is considered to lack unity of invention since its subject-matter relates not to one but at least two separate inventions not linked together by a common underlying inventive concept as required by Rule 13.1 PCT.

The claims and the inventions to which the at least two separate inventions relate may be grouped according to the isoforms of IG20, each isoform being considered to be one presumed invention. In the claims only IG20 and DENN-SV are mentioned explicitly. However, all claims also refer to splice variants of IG20 and DENN-SV. It seems that at least seven of said different isoforms are known (see e.g. paragraph 90 on page 20 of the description and D2). Hence, presumed invention 1 refers to uses of IG20 (claims 1-7, 14-20), presumed invention 2 to uses of DENN-SV (claims 1-20), presumed invention 3 refers to uses of isoform 3 such as e.g. KIAA0358 and so on (see also lack of clarity objection,

item III,2).

Unity of invention is only accepted if said presumed inventions have the same or a corresponding special technical feature. Special technical features are such features that define the contribution of the claimed invention over the prior art. To identify the presumed contribution to the art, the "problem-solution-approach" is used.

The problem underlying the present application can be formulated as the provision of methods for the regulation of apoptosis. The solution consisting in the use of isoforms of IG20 is not novel in view of either D1 or D2. D1 discloses that HeLa cells stably transfected with the isoform IG20 showed enhanced susceptibility to TNF-alpha-induced apoptosis, whereas cells transfected with DENN-SV showed resistance. Hence the use of splice variants of the gene *IG20* for the regulation of apoptosis can not be considered to be the contribution to the art. The same applies in view of D2. No other common inventive concept could be identified.

No further search fees have been requested, since search and examination could be performed the effort not justifying further fees. However, the Applicant has to expect a non-unity objection during examination in national and regional procedures.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-8, 11, 19, and 20 is not new in the sense of Article 33(2) PCT.

Claims 1-4 and 7 refer to the use (preferably overexpression) of the splice variant IG20 for the regulation of cell death and in particular, to the increase of cell death of cancer cells (see also objections under item III, 2).

Claims 8 and 11 refer to the use of DENN-SV or splice variants of DENN-SV for the regulation of cell death, in particular to the promotion of growth of cells and to the prolongation of cell life.

D1 discloses that IG20, KIAA0358, MADD/DENN, and DENN-SV are different splice variants of the gene *IG20* and shows that stable transfection of HeLa cells with the splice variant IG20 enhances susceptibility to TNF-alpha-induced apoptosis, whereas cells transfected with DENN-SV were resistant to apoptosis.

D2 is an abstract disclosing that IG20 is expressed in seven different isoforms in various combinations in both normal and cancer cells and tissues. Furthermore, it is disclosed that transfection of HeLa cells with the IG20-isoform enhances TNF-alpha induced apoptosis, while the isoform DENN-SV induced resistance to apoptosis.

Hence, the subject-matter of claims 1-4, 7, 8 and 11 is not novel either in view of D1 or D2.

Furthermore, the use of IG20 to increase sensitivity to cell death induced by radiation or chemotherapy according to claims 5 and 6 is not novel in view of D2, since D2 already discloses that IG20 enhances susceptibility to apoptosis when cells were treated with vinblastin, etoposide, or gamma irradiation.

The subject-matter of claims 19 and 20 lacks novelty e.g. in view of D1 or D2. As it is already clear from the formulation of the claims and the description (reference to database accession numbers!), that the nucleic acid sequences encoding splice variants of IG20 are well known in the art.

2. Inventive step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 9, 10, 12, and 16-18 does not involve an inventive step in the sense of Article 33(3) PCT.

Claims 9, 10, and 16-18 refer to the use of SiRNA, anti-sense molecules and antibodies to IG20 or a splice variant thereof for the regulation of cell death (see also item III,2). Since

the function of IG20 and of its splice variants was already known (see e.g. D1 and D2) and SiRNA, anti-sense molecules and antibodies are known to inhibit the function of the corresponding protein, the subject-matter of the above-mentioned claims is obvious in view of D1 or D2 in combination with the general knowledge.

Claim 12 refers to the regulation of cell death in insulin producing cells, neuronal cells, and stem cells. The listed cells seem to be an arbitrary selection of all known cells and therefore, obvious.

3. Further observations

The Applicant seems to consider the contribution to the art to be the medical use of the splice forms of the gene *IG20*, in particular of the splice variants IG20 and DENN-SV.

However, neither the original claims nor the amended claims are limited to medical uses: The method claims of the original and amended claims are also directed to *in vitro* uses and the composition according to amended claims 1-10 could be simply understood to be a composition comprising the splice form in water or buffer. Non-medical uses and such compositions lack novelty (see above).

Assuming that the claims were limited to medical uses of the splice forms, the subject-matter of such limited claims does not seem to be inventive. It seems possible to predict from the effect of the splice variants IG20 and DENN-SV on HeLa cells, which is disclosed in D1, that said splice variants may be used as a medicament. In fact, the results disclosed in D1 with the commonly used cell culture system of HeLa cells and using TNF-alpha to induce apoptosis seems to be an invitation to study also other cell culture systems and *in vivo* applications. The fact that TNF-alpha can not be used *in vivo* does not lead away from possible medical uses, since the skilled practitioner is aware of other possibilities to induce apoptosis *in vivo*. Said opinion is confirmed by D2, which discloses other options to induce apoptosis which can also be applied *in vivo*, such as vinblastin, etoposide and gamma irradiation. Therefore, even claims limited to medical uses do not seem to be inventive in view of the disclosure of D1 and D2 alone or in combination.

Int'l Appl. No. PCT/US 2004/030986

Attorney Docket No. 21726-97440

SUBSTITUTE PAGES

CLAIMS:

- [C1] A composition used to alter the balance in cells between levels of splice variants of the gene *IG20* to increase or decrease apoptosis, the composition comprising a molecule selected from the group consisting of the splice variant *IG20*, a fragment of *IG20*, an agent increasing *IG20* levels, and an agent decreasing *DENN-SV* levels, if apoptosis is to be increased, or selected from the group consisting of *DENN-SV*, a fragment of *DENN-SV*, and an agent increasing *DENN-SV* levels, if apoptosis is to be decreased.
- [C2] The composition of claim 1 wherein cells are contacted with an apoptosis-inducing agent.
- [C3] The composition of claim 2, wherein the agent is radiation.
- [C4] The composition of claim 2, wherein the agent is a chemotherapeutic agent.
- [C5] The composition of claim 1 wherein the agent decreasing *DENN-SV* levels is an anti-sense molecule against *DENN-SV* or a fragment thereof.
- [C6] The composition of claim 1 wherein the agent decreasing *DENN-SV* levels is an Si RNA against a middle portion of *DENN-SV*.
- [C7] The composition of claim 1 wherein the molecule is an antibody against *IG20* or *DENN-SV* or a fragment thereof.
- [C8] The composition of claim 1, wherein the cells are in a tumor.
- [C9] The composition of claim 2, wherein apoptosis-inducing agent is a ligand that binds to a death receptor.
- [C10] The composition of claim 9, wherein the ligand for the death receptor is selected from the group consisting of FAS-ligand, TRAIL, and anti-receptor antibodies.
- [C11] A method to alter the balance of splice variants *IG20* *DENN-SV* or *IG20* of the gene, or a combination thereof, to regulate cell death or cell proliferation, the method comprising:
- (a) determining endogenous levels of at least one of the splice variants;
and
 - (b) providing a molecule to cells to regulate the endogenous levels of at least one of *IG20* and *DENN-SV*, wherein the molecule is an antibody, anti-sense or Si RNA against one of the splice variants, that alters the balance.

Int'l. Appl. No. PCT/US 2004/030986

Attorney Docket No. 21726-97440

- [C12] The method of claim 11, wherein the molecule is further defined as selected from the group consisting of a chemical regulator, genetic sequence, cDNA, oligonucleotide, protein, and peptide.
- [C13] The method of claim 11 wherein the molecule is IG20 administered in conjunction with chemotherapy.
- [C14] The method of claim 13 wherein cells are made more sensitive to TRAIL induced apoptosis.
- [C15] A method to modulate signaling pathways that affect cell death or cell replication, the method comprising:
- (a) selecting splice variants of *IG20* that affect signaling pathways; and
 - (b) modulating the pathway of cell death or cell proliferation by altering the express of selected splice variants of the *IG20* gene.
- [C16] The method of claim 15 wherein the signaling pathways are JNK or MAP kinase pathways.